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Reply

Sirs

The debate over the potential harmful effects of silicone from breast implants has persisted for more than a decade (1). The case reported by Caramashi *et al*. (2) provides further evidence regarding a potential relationship between silicone spread from breast implants and dermatomyositis. Interestingly, one of two class II haplotypes in the case reported by the authors was identical to the two patients we have reported earlier (3). In our opinion, these findings support the hypothesis of a predisposing genetic background. It is well recognized that several HLA alleles are related to autoimmune diseases. Dermatomyositis and anti-synthetase antibodies have been associated with HLA-DRB1 and DQA1 alleles (4), as was the case in our patients. Class II HLAis involved in the process of antigen presentation to CD4 T cells in the humoral immune response and silicone may act as a hapten-like substance and combine with other molecules to form an antigenic complex. It would be of interest to know if the patient reported by Caramashi *et al*. was positive for anti-synthetase antibodies.

Although epidemiological studies have failed to demonstrate a clear association between connective tissue disorders and silicone breast implants, clinicians have sometimes felt that in specific cases, silicone may act as a factor for human adjuvant disease factor in patients with a predisposing genetic background. The case reported by Caramashi *et al*. lends support to this hypothesis. The scarce number of patients with dermatomyositis (prevalence of 3-4 cases per million inhabitants) could explain in part the lack of association in epidemiologic studies. Low- or medium-molecular-weight polymers have been known to migrate from the intact silicone elastomer shells into surrounding tissues in a process known as a "gel bleeding" (5). The assay of low- molecular-weight silicones in plasma and blood using chromatographic techniques is probably the best way to demonstrate the relationship between silicone and disease (6). Work is currently underway to determine these parameters in our patients.

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Coexistence of non-specific and usual interstitial pneumonia in a patient with severe cystic scleroderma lung involvement and parvovirus B19 infection

Sirs,

Scleroderma lung disease (SLD) is one of the most frequent clinical manifestations of systemic sclerosis (SSc) (1-3). Recently, we observed a very severe SLD characterised by the coexistence of nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), and diffuse parenchymal cyst formation.

A 25-year-old woman was referred to our Rheumatology Unit in March 2003 because of 2-year history of Raynaud's phenomenon and recent onset ulceration of the second finger of the left hand. The diagnosis of SSc was made on the basis of the physical examination (acrocyanosis, swollen hands, with digital pitting scars and mild sclerodactyly, melanoderma, and microstomia), 'active' scleroderma pattern on capillaroscopy, presence of anti-centromere antibodies (titre 1: 160), and mild bibasilar interstitial involvement on standard chest x-ray (Fig. 1a). Surprisingly, high resolution computed tomography (HRCT) showed the presence of multiple, disseminated cysts in lung parenchyma (Fig. 1c), reminiscent of lymphoangioleiomyomatosis (LAM) (4). Spirometry revealed a restrictive pattern (forced vital capacity 54% of predicted) with marked reduction of lung diffusion capacity (23% of predicted).

One month later the patient developed exertion dispnoea. Chest examination revealed crackles (velcro rales) over the bases in both lungs. Bronchoalveolar lavage (BAL) showed an active alveolitis (eosinophil 29%, n.v. 0%; lymphocyte 14%, n.v. 6.8 ± 1.3), while desmin and HMB45 immunoreactive cells were absent.

In order to exclude LAM, two lung biopsies (lingula and inferior lobe) were carried out

by means of video-assisted thoracoscopy followed, 20 days later, by pneumothorax (left lung), which resolved after adequate drainage. Light microscopy examination of the two lung specimens revealed the coexistence of NSIP and UIP (Fig. 1e, f). Thus, the hypothesis of LAM was definitely excluded on the basis of the histologic findings and the negative HMB 45 findings.

Direct immunofluorescence studies revealed IgG fine granular staining of the septal microvasculature with endothelial cell localisation, IgM focal granular vascular staining, striking granular nuclear and mural staining of the septal capillaries for C4d, and focal weak vascular deposition for C5-9 within the bronchial wall. Electron microscopic examination confirmed the presence of highly fibrotic and thickened septa permeated by inflammatory cells comprising mainly lymphocytes and monocytes with a smaller number of mast cells and few plasma cells. The endothelial cells were swollen, and the capillary basement membranes were thickened with striking lamination.

Virological studies showed circulating anti-parvovirus B19 (PV-B19) antibodies, IgG type (EIA, Biotrin, EIRE); moreover, in the lung tissue PV-B19 DNAwas demonstrated by means of both solution phase PCR and ISH, as previously described (5, 6).

Given the presence of active alveolitis, the patient was treated with monthly pulse cyclophosphamide (500 mg/square meter b.s.; cumulative dosage of 11 g) and 6-methylprednisolone (16 mg/day). However, the patient's clinical, functional, and radiological (Fig. 1b, d) manifestations did not improve. Due to the severity of the lung involvement, which was unresponsive to immunosuppressive treatment, a possible lung transplant was taken into consideration.

The case described here shows some important peculiarities: the uncommon presentation of diffuse cystic pulmonary involvement (7,8), radiographically mimicking a LAM (4); coexistence of two prognostically different histological patterns of SLD; presence of eosinophilic alveolitis unresponsive to immunesuppressive treatment; and possible role of PV-B19 infection.

The NSIP pattern is more frequent in SLD; it is characterized by a relatively more benign course if compared to the UIPtypically found in idiopathic pulmonary fibrosis (2, 3). The case here described is the first observation of SLD with both NSIP and UIP, as recently demonstrated for idiopathic pulmonary fibrosis by means of multiple lung biopsies (2,3,10). The coexistence of these histological patterns may represent different evolutive stages of the same pathogenetic process (2,3,10); this particular association shows the same worse prognosis observed in patients with only UIP alterations (10).

The rapid impairment of lung involvement, despite the timely introduction of cyclophosphamide, can be related, at least in part, to the high concentration of eosinophils in the BAL (2). In this context, the possible contribution of PV-B19 infection cannot be ruled out. Given its biological properties, namely the tropism for both endothelia and fibroblasts, this virus may play a role in the pathogenesis of SSc (5,6, 11,12), as indirectly suggested by either persistent viral infection and immune deposits within altered lung structures.

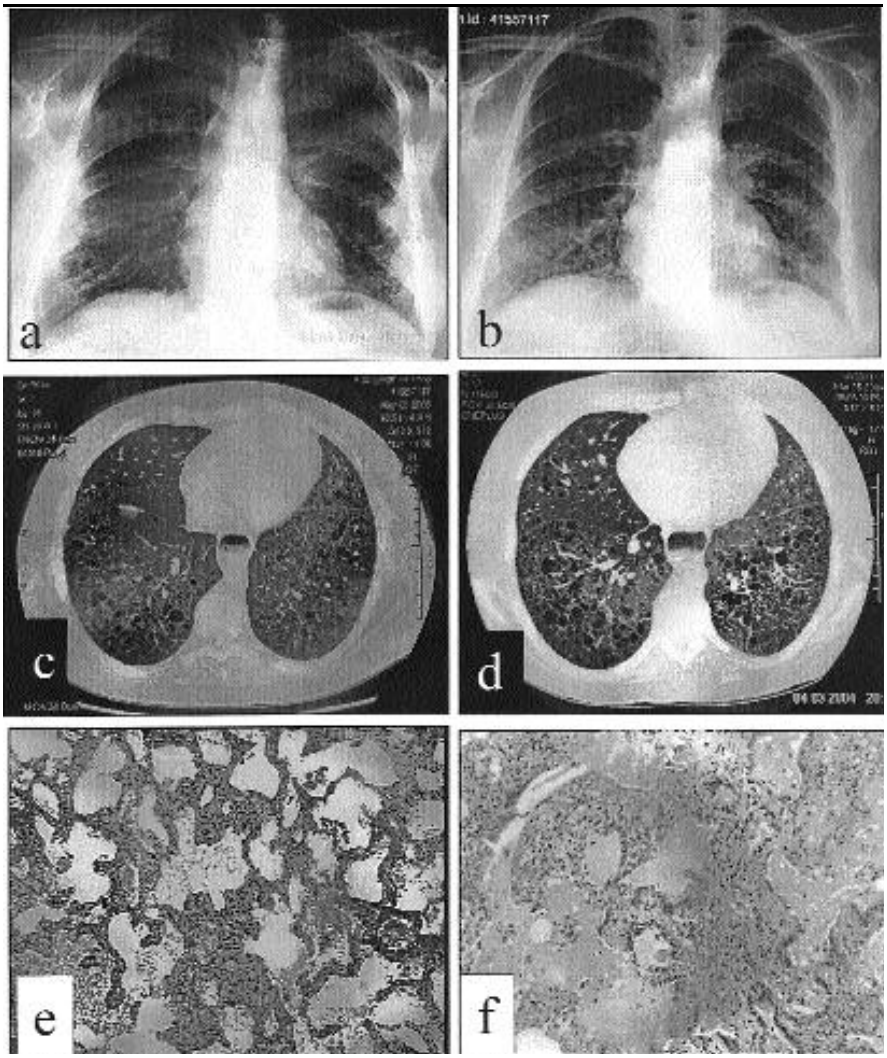

Fig. 1. (**a**) Chest x-ray at the time of the patient's presentation shows mild interstitial involvement.
(**b**) Chest x-ray 1 year later showing marked increase of lung interstitial involvement.
(**c**) High resolution computed tomography (HRCT) at the time of the patient's presentation: presence of multiple, disseminated cysts in lung parenchyma, ranging in diameter from a few millimeters to 1 cm. The cysts involved almost the entire lung, particularly the inferior lobes, but also apical and anterior areas of the middle and superior lobes with mild interstitial involvement. HRCTfindings suggested the diagnosis of lymphangioleiomiomatosis.
(**d**) HRCTone year later: cystic and fibrotic lesions became more diffuse, with severe architectural damage of the lungs.
(**e**) Non-specific interstitial pneumonia (NSIP) pattern in the lingula bioptic specimen: homogeneous expansion of the interalveolar septae by collagen with vascular drop out and concomitant permeation of the interstitium by a modest mononuclear cell infiltrate.
(**f**) Presence of the typical interstitial pneumonia (UIP) pattern in the inferior lobe: temporal heterogeneity of the lesions, presence of fibroblast aggregates with active fibrosing process, honey-combing, alveolar epithelization, and some vascular hypertensive changes.

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